COUGH REMEDIES - Antitussives (Oskar Bub, Ludwig Friedrich)

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2. Antitussives

2.1. Antitussives Acting on the Central Nervous System

Antitussives chiefly act on the central nervous system (CNS). They reduce the number and intensity of coughing bouts by inhibiting the cough reflex in the cough center of the brain stem or by blocking sensitive receptors in the bronchi.

Morphine, codeine, and narcotine, isolated from opium (→ Alkaloids), were the first compounds of this group to be used. In addition to their analgesic effect, these drugs also have an antitussive potency. Morphine is not suited for use as an antitussive because of its adverse effects (respiratory depression, constipation, addictive potential). Its analgesic potency and side effects were attenuated by etherifying its phenolic hydroxyl group (→ Analgesics and Antipyretics), but its antitussive potency was not affected by this substitution.

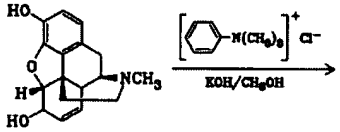
The methyl ether codeine is the most popular antitussive today. Other morphine ethers have also been used as antitussives (e.g., ethylmorphine or pholcodine).

Chemical modification of the morphine nucleus has led to derivatives of greater analgesic and antitussive activity, but these derivatives still have morphine-like side effects (e.g., dihydrocodeine or hydrocodone). Total synthesis of the morphine skeleton by Grewe in 1946 made the morphinans accessible; their (+)-isomers are potent antitussives that do not lead to addiction.

2.1.1. Alkaloids and Derivatives (→ Alkaloids)

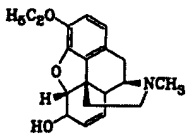
Codeine[*76-57-3*] , $C_{18}H_{21}NO_3$, M_r 299.36; monohydrate [*6059-47-8*] , M_r 317.38, *mp* 154 – 156 °C, $[\alpha]_D^{15}$ – 136° (*c* = 2; ethanol); hydrochloride dihydrate [*1422-07-7*] , $C_{18}H_{22}ClNO_3 \cdot 2\ H_2O$, M_r 371.9, *mp* 280 °C, $[\alpha]_D^{22}$ – 108° (H_2O); phosphate [*52-28-8*] , $C_{18}H_{24}NO_7P$, M_r 397.38; sulfate [*1420-53-7*] , $C_{36}H_{44}N_2O_{10}S$, M_r 696.82.

Codeine occurs naturally in opium (0.3 %), but most of it is prepared by methylation of morphine with trimethylphenylammonium hydroxide [5]:



Trade Names. Codicept (Sanol), Codeinfos (Union Quimico-Farmaceutica), Tricodein (Solco, Zyma), Codipertussin (Taeschner); combinations: Codipront (Mack), Tussoretard (Klinge), Codicaps (Thiemann), Empracet (Burroughs Wellcome), Copavin (Lilly), and many others.

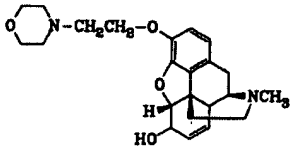
Ethylmorphine [*76-58-4*] , codethyline, dionin, $C_{19}H_{23}NO_3$, M_r 313.38, *mp* 199 – 201 °C; hydrochloride dihydrate [*125-30-4*] , $C_{19}H_{24}ClNO_3 \cdot 2\ H_2O$, *mp* 123 °C (decomp.).



Ethylmorphine is prepared by ethylation of morphine with ethyl benzenesulfonate in the presence of potassium hydroxide [6]. The pharmacological effects of ethylmorphine are very similar to those of codeine; ethylmorphine is slightly less effective as an antitussive [7].

Trade Names. Codethyline (Houdé), Trachyl (Beytout); combinations: Expectorans Solucampher (Delalande), Tussedat (Sagitta).

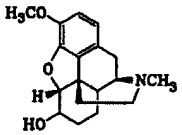
Pholcodine [*509-67-1*] , 3-*O*-(2-morpholinoethyl)morphine, $C_{23}H_{30}N_2O_4$, M_r 398.49, *mp* 91 °C (monohydrate), $[\alpha]_D^{20}$ – 95.3° (*c* = 2; ethanol).



For the synthesis of pholcodine, morphine is alkylated with *N*-(2-chloroethyl)morpholine in the presence of sodium hydroxide [8]. Pholcodine is a centrally acting antitussive of similar potency as codeine; it has minimal side effects and no addictive potential [9].

Trade Names. Ethnine (Allen and Hanburys, Purdue Frederick), Folcodan (L.I.B.S.), Memine (Macfarlan Smith), Tussokon (Pharmacia).

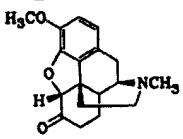
Dihydrocodeine[*125-28-0*] , drocode, $C_{18}H_{23}NO_3$, M_r 301.37, *mp* 112 – 113 °C; hydrogen tartrate [*5965-13-9*] , $C_{22}H_{29}NO_9$, M_r 451.5, *mp* 192 – 193 °C.



Dihydrocodeine is made by catalytic hydrogenation of codeine over platinum, palladium, or nickel catalysts [10] , or by methylation of dihydromorphine with dimethyl sulfate [11]. Dihydrocodeine has antitussive and analgesic properties similar to those of morphine, with fewer side effects [6] , [12].

Trade Names. Paracodin (Knoll), Remedacen (MüllerRorer), Rikodeine (Riker), Tiamon (Temmler; combination).

Hydrocodone[*125-29-1*] , dihydrocodeinone, $C_{18}H_{21}NO_3$, M_r 299.38, *mp* 198 °C; hydrochloride hydrate [*25968-91-6*] , $C_{18}H_{22}ClNO_3 \cdot H_2O$, M_r 353.83, *mp* 185 – 186 °C (decomp.), $[\alpha]_D^{27}$ – 130° (H_2O); bitartrate hemipentahydrate [*34195-34-1*] , $C_{22}H_{27}NO_9 \cdot 2.5\ H_2O$, M_r 494.5.

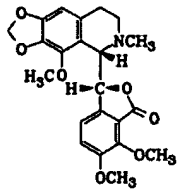


For the synthesis of hydrocodone, codeine is catalytically rearranged by heating with palladium or platinum in alcoholic or aqueous acidic solution [13]. For other methods of preparation, see [3vol. 1, p. 120]. Hydrocodone is a stronger antitussive and analgesic than codeine, but it also has morphine-like side effects and addictive potential [6].

Trade Names. Dicodid (Knoll), Didrate (Penick), Novocodina (Erba); numerous combinations.

Noscapine[*128-62-1*] , narcotine,

(3 *S*)-6,7-dimethoxy-3-[(1 *R*)-1,2,3,4-tetrahydro-8-methoxy-2-methyl-6,7-methylenedioxy-1-isoquinoly $C_{22}H_{23}NO_7$, M_r 413.43, *mp* 176 °C; hydrochloride monohydrate [*912-60-7*] , $C_{22}H_{24}ClNO_7 \cdot H_2O$, M_r 467.9, *mp* 200 °C (decomp.).

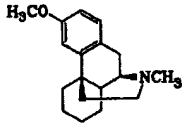


Noscapine is a phthalide alkaloid which occurs in amounts up to about 6 % in opium. It is a centrally acting antitussive of nearly the same potency as codeine, but without morphine-like side effects and with additional bronchodilatory activity [14].

Trade Names. Capval (Dreluso), Lyobex (Lappe), Narcotussin (Biologici, Italia), Tusscapine (Fisons); combinations: Tussoretard (Klinge), Tiamon (Temmler), and many others.

2.1.2. Morphinans

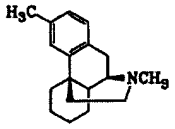
Dextromethorphan[*125-71-3*] , (+)-3-methoxy-*N*-methylmorphinan, $C_{18}H_{25}NO$, M_r 271.41; hydrobromide monohydrate [*6700-34-1*] , $C_{18}H_{26}BrNO \cdot H_2O$, M_r 370.34, *mp* 122 – 124 °C, $[\alpha]_D^{20}$ + 27.6° (*c* = 1.5; H_2O).



Dextromethorphan is made by resolution of (±)-3-hydroxy-*N*-methylmorphinan (racemorphan; → Analgesics and Antipyretics) with d-tartaric acid and subsequent O-methylation of the (+)-isomer with phenyltrimethylammonium hydroxide [15]. Dextromethorphan has an antitussive effect similar to that of codeine with fewer side effects; it does not lead to addiction [16].

Trade Names. Romilar (Hoffmann-La Roche), Cosylan (Parke-Davis), Dormethan (Dorsey), Husmedin (Toho), Methorcon (Kowa); numerous combinations.

Dimemorfan[*36309-01-0*] , 3,17-dimethylmorphinan, $C_{18}H_{25}N$, M_r 255.41, *mp* 90 – 93 °C; phosphate, $C_{18}H_{28}NO_4P$, M_r 353.41, *mp* 267 – 269 °C, $[\alpha]_D^{23}$ + 25.7° (*c* = 0.5; methanol).

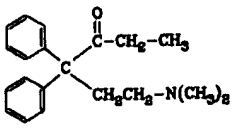


Dimemorfan is prepared by using Grewe's morphinan synthesis [17]. It is 1.5 times as potent an antitussive as dextromethorphan, with some analgesic activity and minimal side effects [18].

Trade Names. Astomin (Yamanouchi), Dastosin (Morrith).

2.1.3. Arylalkylamines

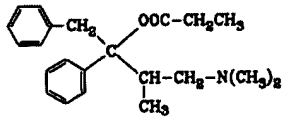
Normethadone [*467-85-6*] , 6-(*N,N*-dimethylamino)-4,4-diphenyl-3-hexanone, $C_{20}H_{25}NO$, M_r 295.42, *bp* 164 – 167 °C (0.4 kPa); hydrochloride [*847-84-7*] , $C_{20}H_{26}ClNO$, M_r 331.88, *mp* 174 – 175 °C.



Normethadone is prepared by the same route used for methadone (→ Analgesics and Antipyretics - 3.1.3. Methadone and Congeners) [19]. Normethadone is twice as potent an antitussive as codeine, but it has reduced analgesic potency compared with methadone, which is also a potent antitussive [20]. Both drugs are rarely used because of their addictive potential.

Trade Name. Ticarda (Hoechst).

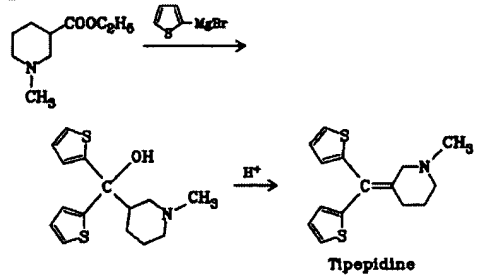
Levopropoxyphene[*2338-37-6*] , (–)-1-benzyl-3-(*N,N*-dimethylamino)-2-methyl-1-phenylpropylpropionate, $C_{22}H_{29}NO_2$, M_r 339.48, *mp* 75 –76 °C, $[\alpha]_D^{25}$ – 68.2° (*c* = 0.6; chloroform); 2-naphthalenesulfonate monohydrate (napsylate) [*55557-30-7*] , $C_{22}H_{29}NO_2 \cdot C_{10}H_8O_3S \cdot H_2O$, M_r 565.72.



Levopropoxyphene is prepared as described for propoxyphene (→ Analgesics and Antipyretics - Dextropropoxyphene), using the (–)-form of the intermediates [21]. Levopropoxyphene has useful antitussive properties, whereas analgesic activity is present mainly in dextropropoxyphene [22].

Trade Names. Novrad (Lilly), Sotorni (Ravensberg).

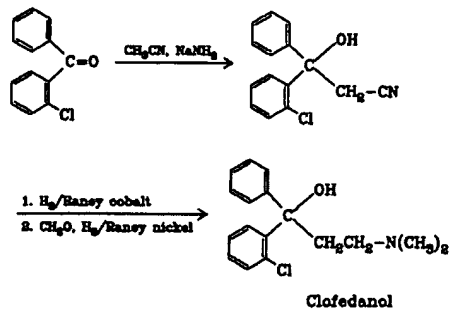
Tipepidine[*5169-78-8*] , 3-(di-2-thienyl-methylene)-1-methylpiperidine, $C_{15}H_{17}NS_2$, M_r 275.45, *mp* 64 – 65 °C; citrate monohydrate [*5169-77-7*] , $C_{21}H_{25}NO_7S_2 \cdot H_2O$, M_r 485.58, *mp* 138 – 139 °C; 4-hydroxybenzophenone-2-carboxylate (hibenzoate) [*31139-87-4*] , $C_{29}H_{27}NO_4S_2$, M_r 517.67, *mp* 187 – 190 °C. Grignard reaction of ethyl 1-methyl-3-piperidinecarboxylate (ethyl 1-methylnipecotate) with 2-thienylmagnesium bromide and acid dehydration of the intermediate carbinol yields tipepidine [23]:



Tipepidine is approximately equipotent to codeine in antitussive activity, but less analgesic and toxic [24].

Trade Names. Asverin (Tanabe), Sotal (G. Ramon).

Clofedanol[*791-35-5*] , chlophedianol, 1-(2-chlorophenyl)-1-phenyl-3-dimethylaminopropanol, $C_{17}H_{20}ClNO$, M_r 289.80; hydrochloride [*511-13-7*] , $C_{17}H_{21}Cl_2NO$, M_r 326.26, *mp* 190 – 191 °C. For the synthesis of clofedanol, 2-chlorobenzophenone reacts with acetonitrile in the presence of sodium amide; the nitrile group of the product is then catalytically reduced to the primary amine, and the intermediate is converted into clofedanol by reductive N-methylation [25]:

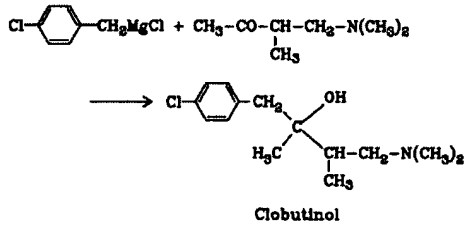


Clofedanol

Clofedanol is a centrally acting antitussive without analgesic activity or morphine-like side effects, but with some of the effects of a local anesthetic [26].

Trade Names. Detigon (Bayer), Pectolitan (Kettelhack Riker), Ulo (Riker), Coldrin (Nippon Shinyaku).

Clobutinol[*14860-49-2*] , 2-(4-chlorobenzyl)-4-dimethylamino-3-methyl-2-butanol, $C_{14}H_{22}ClNO$, M_r 255.79, *bp* 179 – 181 °C (1.6 kPa); hydrochloride [*1215-83-4*] , $C_{14}H_{23}Cl_2NO$, M_r 292.25, *mp* 169 – 170 °C. Clobutinol is made by Grignard reaction of 4-dimethylamino-3-methyl-2-butanone with 4-chlorobenzylmagnesium chloride [27].

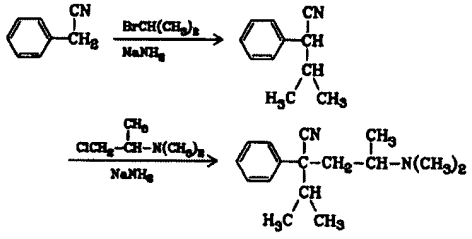


Clobutinol

Clobutinol is an antitussive with CNS activity which is equipotent to codeine and has properties similar to those of clofedanol [28].

Trade Name. Silomat (Thomae, Badrial, Morishita).

Isoaminile[*77-51-0*] , 4-dimethylamino-2-isopropyl-2-phenylvaleronitrile, $C_{16}H_{24}N_2$, M_r 244.37, *bp* 138 – 146 °C (0.4 kPa); citrate [*126-10-3*] , $C_{22}H_{32}N_2O_7$, M_r 436.62, *mp* 63 – 64 °C. For the synthesis of isoaminile, benzyl cyanide is alkylated in two steps, first by isopropyl bromide and then by 2-(dimethylamino)propyl chloride in the presence of sodium amide [29].



Isoaminile

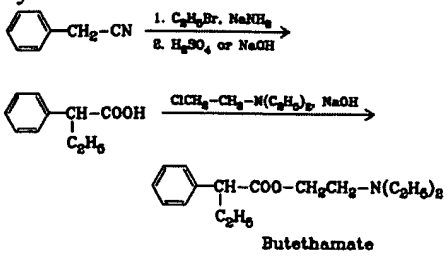
Isoaminile is similar to codeine, but it has no analgesic activity or morphine-like side effects [30].

Trade Names. Peracon (Kali-Chemie), Dimyril (Fisons).

2.1.4. Basic Esters

Butethamate[*14007-64-8*] , 2-diethylaminoethyl 2-phenylbutyrate, $C_{16}H_{25}NO_2$, M_r 263.37, *bp* 167 – 169 °C (1.5 kPa), n_D^{20} 1.4909; citrate [*13900-12-4*] , $C_{22}H_{33}NO_9$, M_r 455.51, *mp* 109 – 110 °C. Butethamate is made by alkylation of benzyl cyanide with ethyl bromide in the presence of sodium

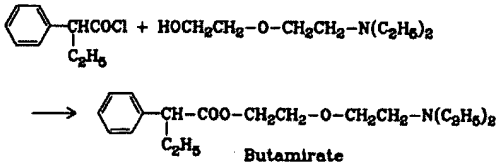
amide; subsequent hydrolysis of the nitrile group yields 2-phenylbutyric acid, which is then esterified by reaction of the sodium salt with 2-diethylaminoethyl chloride [31].



In addition to its antitussive activity, butethamate is active as a bronchodilator [32].

Trade Name. Pertix (Hommel); in many combination drugs.

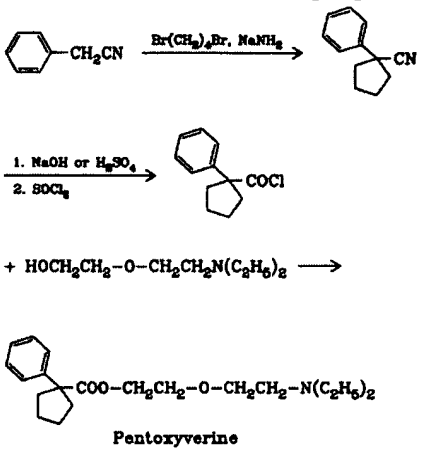
Butamirate[*18109-80-3*] , 2-(2-diethylaminoethoxy)ethyl 2-phenylbutyrate, $C_{18}H_{29}NO_3$, M_r 307.44, *bp* 140 – 155 °C (0.13 kPa); citrate [*18109-81-4*] , $C_{24}H_{37}NO_{10}$, M_r 499.57, *mp* 75 °C. For the synthesis of butamirate, 2-phenylbutyric acid (prepared as described for butethamate) is esterified by reaction of its acid chloride with 2-(2-diethylaminoethoxy)ethanol [33].



Compared to butethamate, the antitussive activity of butamirate is increased because of the lengthening of the side chain.

Trade Names. Acodeen (Hommel), Sinecod (Hommel, Karlspharma), Intussin (Spofa).

Pentoxyverine[*77-23-6*] , carbetapentane, 2-(2-diethylaminoethoxy)ethyl 1-phenyl-1-cyclo-pentanecarboxylate, $C_{20}H_{31}NO_3$, M_r 333.46, *bp* 165 – 170 °C (0.001 kPa); citrate [*23142-01-0*] , $C_{26}H_{39}NO_{10}$, M_r 525.60, *mp* 93 °C. Pentoxyverine is made by alkylation of benzyl cyanide with 1,4-dibromobutane in the presence of sodium amide; subsequent hydrolysis of the nitrile group gives 1-phenylcyclopentanecarboxylic acid, which is then esterified in a procedure analogous to that used for butamirate [34].

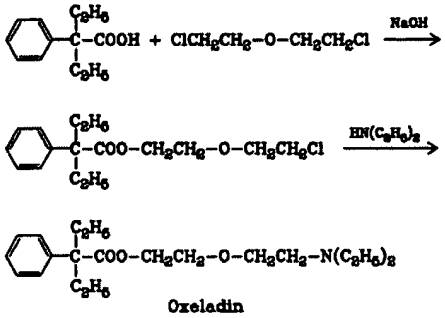


Pentoxyverine is more active than codeine; it has a low toxicity and shows no adverse side effects [35].

Trade Names. Atussil (Squibb), Germapect (Thiemann), Sedotussin (UCB), Toclase (Pfizer, Sumitomo), Tuclase (UCB).

Oxeladin[*468-61-1*] , 2-(2-diethylaminoethoxy)ethyl 3-phenyl-3-pentanecarboxylate,$C_{20}H_{33}NO_3$, M_r

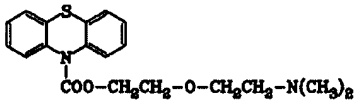
335.47, *bp* 140 °C (0.015 kPa); citrate [*16485-39-5*] , $C_{26}H_{41}NO_{10}$, M_r 527.61, *mp* 90 – 91 °C. For the synthesis of oxeladin, 2-ethyl-2-phenylbutyric acid (prepared in the same way as phenylbutyric acid, see butamirate) is condensed with bis(2-chloroethyl) ether in the presence of sodium hydroxide, and the product is subsequently treated with diethylamine [36].



The pharmacological properties of oxeladin are very similar to those of pentoxyverine [37].

Trade Names. Dorex (Woelm), Paxeladine (Beaufour), Pectamol (British Drug Houses, Malesci), Hihustan (Maruko).

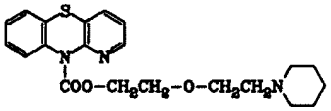
Dimethoxanate[*477-93-0*] , 2-(2-dimethylaminoethoxy)ethyl phenothiazine-10-carboxylate, $C_{19}H_{22}N_2O_3S$, M_r 358.48; hydrochloride [*518-63-8*] , $C_{19}H_{23}ClN_2O_3S$, M_r 394.91, *mp* 161 – 163 °C (decomp.).



Synthesis: phenothiazine-10-carbonyl chloride is obtained by the reaction of phenothiazine with phosgene and then converted to dimethoxanate with 2-(2-dimethylaminoethoxy)ethanol as described for butamirate [38]. Dimethoxanate is a slightly less active antitussive than codeine and shows additional local anesthetic and mucolytic effects [39].

Trade Names. Cotrane (Clin Midy), Cothera (Ayerst), Perlatos (Farmacologico Mil.).

Pipazethate [*2167-85-3*] , 2-(2-piperidinoethoxy)ethyl-10*H*-pyrido[3,2-*b*][1,4]benzothiadiazine-10-carboxylate, pipazetate,$C_{21}H_{25}N_3O_3S$, M_r 399.52; hydrochloride [*6056-11-7*] , $C_{21}H_{26}ClN_3O_3S$, M_r 435.98, *mp* 160 – 161 °C.

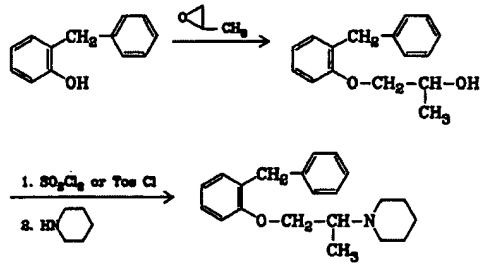


Pipazethate is prepared analogously to dimethoxanate [40]. Pipazethate is predominantly a centrally acting antitussive, similar to dimethoxanate [41].

Trade Names. Selvigon (Homburg, Galenika, Panchemie), Theratuss (Squibb).

2.1.5. Basic Ethers

Benproperine [*2156-27-6*] , 1-[1-(2-benzylphenoxy)-2-propyl]piperidine, $C_{21}H_{27}NO$, M_r 309.43, *bp* 159 – 161 °C (0.03 kPa); phosphate [*3563-76-6*] , $C_{21}H_{30}NO_5P$, M_r 407.45, *mp* 150 – 152 °C.



where Tos = *p*-toluenesulfonyl

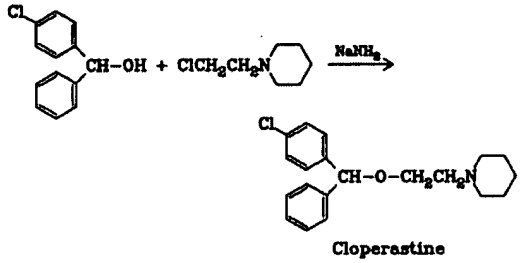
Synthesis: 2-benzylphenol is converted into 1-(2-benzylphenoxy)-2-propanol with propylene oxide; the hydroxyl group of the product is then replaced by chloride or the tosyloxy group and finally by the piperidino group to give benproperine [42].

In addition to its activity on the central nervous system, benproperine also has a peripheral mode of action [43].

Trade Names. Blascorid (Pharmacia, Guidotti), Flaveric (Taito Pfizer), Pectipront (Mack), Tussafug (Robugen, Medipharm).

Cloperastine[*3703-76-2*] , 1-[2-[α-(4-chlorophenyl)benzyloxy]ethyl]piperidine, $C_{20}H_{24}ClNO$, M_r 329.88, *bp* 172 – 174 °C (0.01 kPa); hydrochloride, $C_{20}H_{25}Cl_2NO$, M_r 366.31, *mp* 147.9 °C.

Synthesis: 4-chlorobenzhydrol is condensed with *N*-(2-chloroethyl)piperidine in the presence of sodium amide [44].

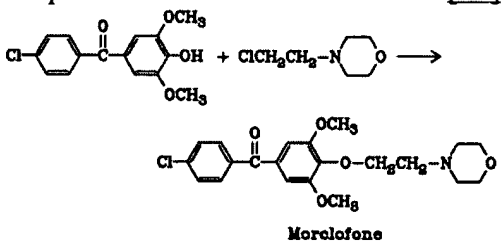


Cloperastine is an antitussive that acts on the central nervous system with nearly the same potency as codeine but with additional antihistaminic and spasmolytic effects [45].

Trade Names. Hustazol (Yoshitomi), Seki (Simes).

Morclofone[*31848-01-8*] , 4′-chloro-3,5-dimethoxy-4-(2-morpholinoethoxy)benzophenone, $C_{21}H_{24}ClNO_5$, M_r 405.88, *mp* 91 – 92 °C. Synthesis:

4-chloro-3,5-dimethoxy-4-hydroxybenzophenone is condensed with *N*-(2-chloroethyl)morpholine in the presence of sodium methoxide [46].

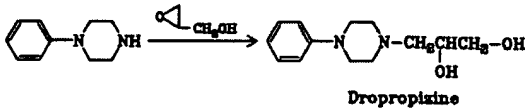


Morclofone is a non-narcotic antitussive with a potency similar to that of codeine [47].

Trade Names. Medicil (Medici), Nitux (Inpharzam), Plausitin (Carlo Erba).

2.1.6. Piperazine Derivatives

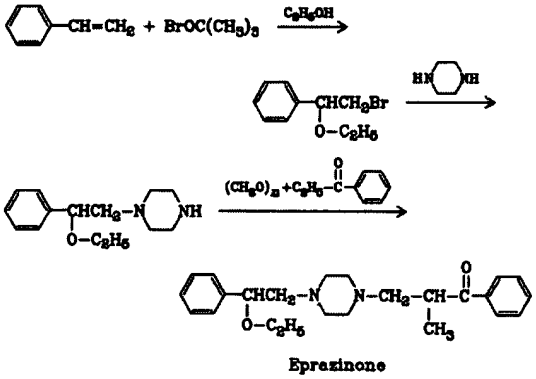
Dropropizine [*17692-31-8*] , 3-(4-phenyl-1-piperazinyl)-1,2-propanediol, $C_{13}H_{20}N_2O_2$, M_r 236.31, *mp* 105 °C; hydrochloride, $C_{13}H_{21}ClN_2O_2$, M_r 272.78, *mp* 142 °C. Dropropizine is made by reaction of *N*-phenylpiperazine with oxiranylmethanol [48].



Dropropizine is nearly as potent an antitussive as codeine and has no adverse side effects [49].

Trade Names. Catabex (Bios-Coutelier), Ribex (Formenti), Larylin (Beiersdorf; combination).

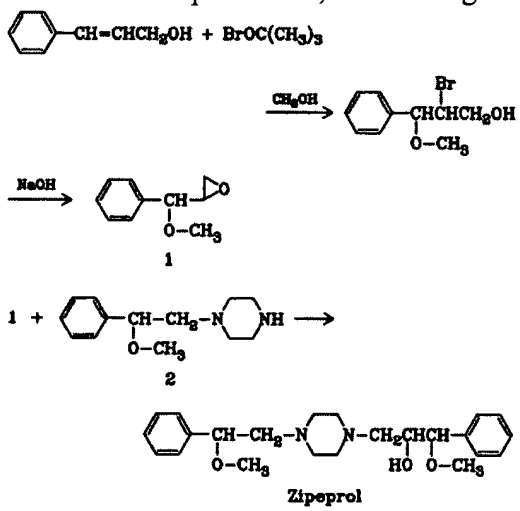
Eprazinone[*10402-90-1*] , 3-[4-(β-ethoxy-2-phenethyl)-1-piperazinyl]-2-methylpropiophenone, $C_{24}H_{32}N_2O_2$, M_r 380.53, *mp* 160 °C; dihydrochloride [*10402-53-6*] , $C_{24}H_{34}Cl_2N_2O_2$, M_r 453.46. Synthesis: styrene is treated with *tert*-butyl hypobromite in ethanol to give 2-ethoxy-2-phenylethyl bromide, which is then converted into eprazinone by exchange of bromine with piperazine and subsequent Mannich reaction with propiophenone and paraformaldehyde [50].



In addition to its antitussive activity, eprazinone has mucolytic potency [51].

Trade Names. Eftapan (Merckle), Mucitux (Rion, Recordati), Resplen (Chugai).

Zipeprol[*34758-83-3*] , 1-methoxy-3-[4-(β-methoxyphenethyl) piperazin-1-yl]-1-phenylpropan-2-ol, $C_{23}H_{32}N_2O_3$, M_r 384.52, *mp* 83 °C; dihydrochloride [*34758-84-4*] , $C_{23}H_{34}Cl_2N_2O_3$, M_r 457.45, *mp* 231 °C. Zipeprol is made by the reaction of **1** with **2**, both of which are obtained in the manner described for eprazinone; the starting material for **1** is 3-phenylallyl alcohol [52].

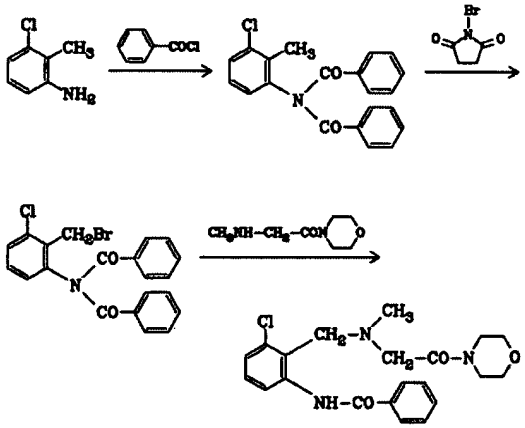


The pharmacological profile of zipeprol is similar to that of eprazinone [53].

Trade Names. Mirsol (Mepha), Respilene (Rete-France, Organon, Winthrop).

2.1.7. Other Compounds

Fominoben [*18053-31-1*] , 3′-chloro-2′-{*N*-methyl-*N*-[(morpholinocarbonyl)methyl]-aminomethyl}benzanilide, $C_{21}H_{24}ClN_3O_3$, M_r 401.89, *mp* 122.5 – 123 °C; hydrochloride [*18053-32-2*] , $C_{21}H_{25}Cl_2N_3O_3$, M_r 438.36, *mp* 206 – 208 °C (decomp.). Synthesis: 3-chloro-2-methylaniline is acylated with benzoyl chloride to give the *N,N*-dibenzoylamine, which is then brominated with *N*-bromosuccinimide and subsequently converted with sarcosine morpholide into fominoben with elimination of one benzoyl group [54].

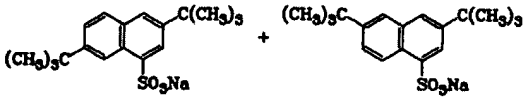


Fominoben

Fominoben has the same antitussive potency as codeine but no analgesic properties or morphine-like side effects. In contrast to the structurally related bromhexine (see Section 3.2.2. Benzylamines), it shows no secretolytic or broncholytic activity [55].

Trade Names. Noleptan (Thomae), Deronyl (VEB Radebeul), Terion (Lusofarmaco).

Sodium dibunate is a mixture of the sodium salts of 3,7- and 3,6-di-*tert*-butyl-1-naphthalenesulfonic acid (dibunate, $C_{18}H_{24}O_3S$, M_r 319.45, *mp* 158 °C); the sodium salt [*14992-59-7*] , $C_{18}H_{23}NaO_3S \cdot 2\ H_2O$, M_r 360.46, melts at 300 °C (decomp.).



Dibunate is obtained by sulfonation of 2,7-di-*tert*-butylnaphthalene with chlorosulfuric acid. The reaction is accompanied by partial rearrangement of one *tert*-butyl group [56]. Dibunate was originally developed as a surfactant and is structurally unrelated to any other antitussive. It has a safe and effective antitussive action, predominantly on the central nervous system [57].

Trade Names. Becantex (Labaz), Bechisan (Sidus); combinations: Aspekton (Krewel), Makatussin (Makara).

⇨ Continued ...

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[5] : C. H. Boehringer, DE 247 180, 1912.J. Schwyzer: *Die Fabrikation pharmazeutischer u. chemisch-technischer Produkte,* Springer, Berlin 1931, p. 389.

Return to Article

[6] : E. Merck AG, DE 131 980, 1902.

Return to Article

[7] : H. Friebel, C. Reichel, A. v. Graevenitz, *Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol.* **224** (1955) 384.

Return to Article

[8] : P. Chabrier, R. Guidicelli, J. Thuillier, *Ann. Pharm. Fr.* **8** (1950) 261.Lab. Dausse, US 2 619 485, 1952.

Return to Article

[9] : A. J. May, J. G. Widdicombe, *Br. J. Pharmacol. Chemother.* **9** (1954) 335.C. E. Heffron, *J. New Drugs* **1** (1961) 217.

Return to Article

[10] : A. Stein, *Pharmazie* **10** (1955) 180.H. Oldenberg, B. Oldenberg, DE 260 233, 1913.

Return to Article

[11] : Knoll AG, DE 278 111, 1914.

Return to Article

[6] : E. Merck AG, DE 131 980, 1902.

Return to Article

[12] : B. Weiss, *Am. J. Pharm.* **31** (1959) 286.

Return to Article

[13] : Knoll AG, DE 607 931, DE 617 238, DE 623 821 (1935).

Return to Article

[3] : G. Erhart, H. Ruschig: *Arzneimittel, Entwicklung, Wirkung, Darstellung,* **vol. 3,** Verlag Chemie, Weinheim 1972, pp. 42 – 62.

Return to Article

[6] : E. Merck AG, DE 131 980, 1902.

Return to Article

[14] : J. La Barre, H. Plisnier, *Arch. Int. Pharmacodyn. Ther.* **119** (1959) 205.M. S. Segal, *JAMA J. Am. Med. Assoc.* **169** (1959) 1063.

Return to Article

[15] : O. Schnider, A. Grüssner, *Helv. Chim. Acta* **34** (1951) 2211;Hoffmann-La Roche, US 2 676 177, 1954.

Return to Article

[16] : B. Pellmont, H. Bächtold, *Schweiz. Med. Wochenschr.* **84** (1954) 1368.

Return to Article

[17] : Yamanouchi, DE 2 128 607, 1971.

Return to Article

[18] : M. Murakami, S. Kawahara, N. Inukai, N. Nagano, H. Iwamoto, H. Ida, *Chem. Pharm. Bull.* **20** (1972) 1706.

Return to Article

[19] : M. Bockmühl, G. Erhart, *Justus Liebigs Ann. Chem.* **561** (1948) 52.

Return to Article

[20] : K. L. Buchheim, B. Angermann, *Dtsch. Med. Wochenschr.* **76** (1951) 1278.

Return to Article

[21] : A. Pohland, H. R. Sullivan, *J. Am. Chem. Soc.* **75** (1953) 4458; **77** (1955) 3400.

Return to Article

[22] : E. B. Robbins, J. A. Miller, *Pharmacologist* **2** (1960) 98.

Return to Article

[23] : K. Okumara, T. Tanaka, S. Siato, H. Kugita, N. Sugimoto, *Chem. Abstr.* **53** (1959) 10 214 g.

Return to Article

[24] : K. Higaki, T. Danno, Y. Kowa, N. Sugimoto, *Chem. Abstr.* **54** (1960) 3725 h.

Return to Article

[25] : Bayer, DE 1 083 277, 1960.

Return to Article

[26] : R. Gösswald, *Arzneim. Forsch.* **8** (1958) 550.

Return to Article

[27] : Thomae, DE 1 146 068, DE 1 153 380, 1959.

Return to Article

[28] : R. Engelhorn, *Arzneim. Forsch.* **10** (1960) 785.

Return to Article

[29] : Kali Chemie, GB 822 695, 1959.

Return to Article

[30] : D. Krause, *Arzneim. Forsch.* **8** (1958) 553.

Return to Article

[31] : Hommels Haematogen, CH 291 375, 1953.Chem. Fabrik Para, CH 292 596, 1953.

Return to Article

[32] : B. N. Halpern, *Arch. Int. Pharmacodyn. Ther.* **59** (1938) 149.

Return to Article

[33] : Hommel AG, DE 1 151 515, 1963.

Return to Article

[34] : H. G. Morren, GB 753 779, 1956.

Return to Article

[35] : S. Levis, S. Preat, F. Moyeroons, *Arch. Int. Pharmacodyn. Ther.* **103** (1955) 200.

Return to Article

[36] : V. Petrow, O. Stephenson, A. M. Wild, *J. Pharm. Pharmacol.* **10** (1958) 40.

Return to Article

[37] : A. David, F. Leith Ross, D. K. Vallance, *J. Pharm. Pharmacol.* **9** (1957) 446.

Return to Article

[38] : Am. Home Prod. Corp., US 2 778 824, 1957 (C. v. Seemann).

Return to Article

[39] : C. I. Chappel, M. G. P. Stegen, G. A. Grant, *Can. J. Biochem. Physiol.* **36** (1958) 475.

Return to Article

[40] : W. A. Schuler, H. Klebe, A. v. Schlichtegroll, *Justus Liebigs Ann. Chem.* **673** (1964) 102.

Return to Article

[41] : K. J. Hahn, H. Friebel, *Med. Pharmacol. Exp.* **14** (1966) 87.

Return to Article

[42] : Aktieselskabet Pharmacia, GB 914 008, 1962.

Return to Article

[43] : K. Yamatsu et al., *Jpn. J. Pharmacol.* **17** (1967) 538.

Return to Article

[44] : Parke, Davis, GB 670 622, 1952.

Return to Article

[45] : K. Takagi, T. Yuizono, Y. Kasé, *Chem. Abstr.* **67** (1967) 107 101 u.

Return to Article

[46] : Carlo Erba, DE 2 016 770, 1971.

Return to Article

[47] : E. Bosisio, G. Casadonte, G. Sacchetti, *Farmaco Ed. Prat.* **26** (1971) 356.

Return to Article

[48] : H. G. Morren, BE 601 394, 1961.

Return to Article

[49] : P. R. B. Noel, *Arzneim. Forsch.* **19** (1969) 1246. K. Cartwright, J. L. Paterson, *J. Pharm. Pharmacol.* **23** (1971) 247.

Return to Article

[50] : C.E.R.M., US 3 448 192, 1969 (R. Mauvernay).

Return to Article

[51] : J. Vacher, C. Lakatos, G. Rispat, P. Duchene-Marullaz, *Arch. Int. Pharmacodyn. Ther.* **165** (1967) 1.

Return to Article

[52] : C.E.R.M., US 3 718 650, 1973 (R. Mauvernay et al.).

Return to Article

[53] : G. Rispat, H. Burgi, D. Cosnier, P. Duchene-Marullaz, G. Streichenberger, *Arzneim. Forsch.* **26** (1976) 523.

Return to Article

[54] : G. Krüger, J. Keck, O. Zipp, J. Nickl, H. Machleidt, G. Ohnacker, *Arzneim. Forsch.* **23** (1973) 290.

Return to Article

[55] : S. Püschmann, R. Engelhorn, *Arzneim. Forsch.* **23** (1973) 296.

Return to Article

[56] : M. Menard, L. Mitchell, J. Komlossy, A. Wrigley, F. L. Chubb, *Can. J. Chem.* **39** (1961) 729.

Return to Article

[57] : G. R. de Vleeschhouwer, *Arch. Int. Pharmacodyn. Ther.* **97** (1954) 34.

Return to Article